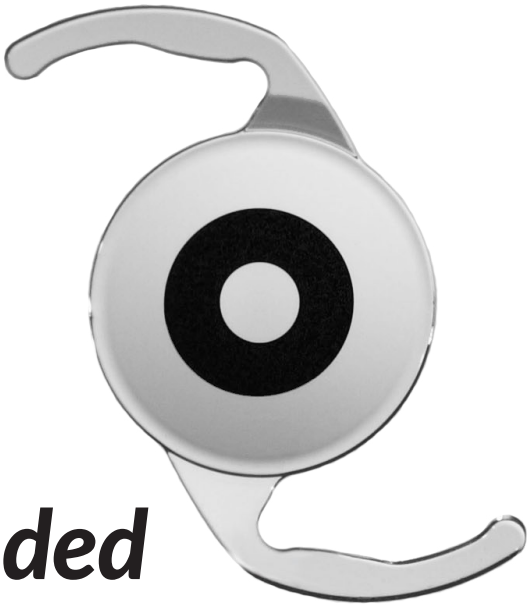
# Cataract & Refractive Surgery:



## *All Eyes on Extended Depth-of-Focus IOLs*

by
MICHAEL LACHMAN,
Contributor

***The cataract and presbyopia surgery markets are turning their attention to new extended depth-of-focus intraocular lenses (IOLs), which have the potential to reinvigorate the premium IOL market by eliminating some of the key drawbacks of current products.***

Cataract surgery is one of the highest-volume surgical procedures, with approximately 3.6 million performed in the US and more than 20 million globally each year. In the US and other developed markets, cataract surgery is typically covered by government and private insurers, including removal of the cataractous crystalline lens and implantation of an artificial intraocular lens (IOL). In these covered/reimbursed procedures, cataract surgery patients are implanted with monofocal IOLs, which provide high-quality distance vision, assuming the surgeon selects an IOL with the appropriate power. However, these standard lenses do not correct for astigmatism and do not provide patients the ability to see clearly at near and intermediate distances.

Over the past decade, premium IOLs have been introduced that deliver refractive benefits not provided by standard IOLs, helping cataract patients to reduce their dependence on spectacles following surgery. Presbyopia-correcting IOLs (PC-IOLs) are premium lenses that provide cataract patients with the ability to see well not only at a far distance but also at near and/or intermediate distances. Toric IOLs are premium IOLs that correct for astigmatism.

Because government and private health insurance plans typically do not cover refractive correction, patients in the US and other developed markets must pay out-of-pocket for these additional products and services. In the US, a policy adopted in 2005 by the Centers for Medicare and Medicaid Services (CMS) enables Medicare patients

to pay an "upcharge" to receive premium refractive services, including toric and PC-IOLs – this was a key factor in the creation of the US premium cataract surgery market.

Outside the US, premium IOL payment policies vary by country. In some markets, patient self-pay policies mirror those in the US; however, many markets still have payment policies that are more restrictive than in the US. For example, in the UK, patients that choose premium IOLs must pay the entire cost of the cataract procedure, not just the additional amount for the premium IOL and physician services related to refractive correction.

In the US, PC-IOLs typically sell for about $800-$1,000, and the average amount paid by patients is about $2,500 per eye, which covers the cost of the IOL plus other refractive services, such as diagnostic tests, provided by physicians. In Europe, PC-IOL prices are lower, typically in the range of $500-$600.

The leading PC-IOLs in the US are the *AcrySof ReSTOR* multifocal IOL (MF-IOL) from **Alcon**, a division of **Novartis AG**; the *Tecnis* MF-IOL from **Abbott Medical Optics** (AMO)/**Abbott Laboratories**; and the *Crystalens* accommodating IOL from **Bausch + Lomb** (B+L), a division of **Valeant Pharmaceuticals Inc.** The *TRULIGN Toric IOL* from B+L, a version of the *Crystalens* that also provides correction for astigmatism, is currently the only approved toric PC-IOL in the US. In Europe and other regions, surgeons have many more approved PC-IOLs from which to choose, including toric versions of the MF-IOLs from Alcon and AMO. Other popular PC-IOLs available outside the US, in both spherical and toric versions, include segmented bifocal IOLs from **Oculentis GmbH** and trifocal IOLs from **Carl Zeiss Meditec AG** and **PhysIOL SA**. In addition to toric versions, several of the leading MF-IOLs outside the US are available in low-add-power versions, which sacrifice some near vision capability in favor of better intermediate vision.

## Global PC-IOL Market Penetration Has Stagnated

When the first PC-IOLs were introduced a decade ago, many industry analysts predicted that market adoption would quickly grow to double-digit penetration rates. However, despite broad PC-IOL availability and incremental product improvements over the past decade, as well as evolving self-pay policies in many countries, market penetration has stalled at mid-single-digit rates in the US and other developed markets. Barriers to greater adoption include:

- **Cost-related barriers:** Out-of-pocket cost to patient of approximately $2,500 per eye, on average, versus traditional cataract surgery, which is fully covered by Medicare and other payors.
- **Surgeon-related barriers:** Reluctance on the part of some surgeons to market premium products and services to cataract patients, given the additional "chair time" involved, high patient expectations, and uncertainty about meeting those expectations.
- **Product-related barriers:** Inability of current PC-IOLs to consistently deliver a full range of near, intermediate, and distance vision with excellent visual quality.

With respect to product-related issues, MF-IOLs simultaneously project a near and far image onto the retina, and the brain chooses the in-focus image while suppressing the out-of-focus image. Halos are caused by the out-of-focus image, and many patients with MF-IOLs find the glare and halos, particularly during night driving, unacceptable. MF-IOLs can provide good near (reading distance) and far visual acuity, but intermediate visual acuity (computer monitor and car dashboard distance) is often lacking, and contrast sensitivity and quality of vision are often compromised. Accommodating IOLs (eg, *Crystalens*) provide good distance and intermediate vision, and good quality of vision, but near vision is often lacking and refractive targeting (choosing the right IOL power to achieve excellent distance vision) is sometimes difficult.

A truly accommodating IOL that provides a full range of near-to-distance vision without any of the drawbacks of MF-IOLs has long been considered the "holy grail" for PC-IOLs. The most advanced product candidate that has the potential to achieve this goal is the *FluidVision* Accommodating IOL from **PowerVision Inc.** This lens has internal fluid channels and relies on natural accommodating forces in the eye to displace fluid in the lens, resulting in a change in lens shape that achieves accommodation in a manner similar to what occurs in the natural lens. A clinical trial of the *FluidVision* lens is underway to support CE mark submission and approval, but the company has not yet initiated its FDA pivotal clinical trial, so availability of this lens in the US is still years away.

## Extended Depth-of-Focus IOLs: Bridging the Gap to True Accommodation

Extended depth-of-focus intraocular lenses (EDOF-IOLs) represent a new product category with the potential to reinvigorate the premium IOL market. EDOF-IOLs are an attempt to bridge the gap between the high optical quality provided by standard monofocal and accommodating IOLs, and the spectacle independence provided by MF-IOLs. Companies developing EDOF-IOLs believe that these lenses have the potential to expand the slow-growing PC-IOL market by eliminating some of the key drawbacks of current products. By significantly reducing the incidence and severity of visual side effects associated with MF-IOLs, such as glare and halos, it is hoped that cataract surgeons will have greater confidence in recommending PC-IOLs for a broad range of patients, including night drivers.

It is too soon to know how each manufacturer will price their EDOF-IOLs. Pricing these lenses below existing PC-IOLs could be market-expanding by lowering the cost barrier to PC-IOL adoption. However, cost is only one of the barriers to PC-IOL adoption, and the IOL itself accounts for only a portion of the cost to the patient. Also, if EDOF-IOLs provide a better overall patient experience than the current offering of PC-IOLs, a case also could be made that these new IOLs should priced on par with or at a premium to current PC-IOLs.

## FDA Recognizes EDOF-IOLs as a New Product Category

In March 2014, the FDA held a workshop on the topic of novel clinical endpoints for premium IOLs. At this meeting, FDA introduced EDOF-IOLs as a new category of premium IOLs intended to "enhance near and intermediate visual performance while having minimum impact on distance performance." The agency noted that EDOF-IOLs could have advantages over MF-IOLs, including a lower incidence of glare and halos and less loss of contrast at distance focus, although visual performance improvement at near may be modest or absent.

The 2014 FDA workshop was the first public forum for discussion of preclinical and clinical testing requirements for EDOF-IOLs, with the ultimate goal of speeding development and approval of future submissions. The FDA acknowledged that there are no current standards, or even draft standards or guidance, for these lenses, and that no approved IOLs in the US have EDOF claims. Challenges in developing clinical requirements for EDOF-IOLs include lack of validation for currently used patient questionnaires, difficulty in objective and subjective measurement of accommodation, and uncertainty regarding acceptable rates of adverse events.

At least three companies – AMO, **AcuFocus Inc.**, and **Hoya Surgical Optics/Hoya Corp.** – have introduced EDOF-IOLs on a limited basis in Europe over the past six months and are planning to bring these lenses to the US in the future. Each of these lenses takes a different optical approach to extending the near-to-far range of vision provided by the lens.

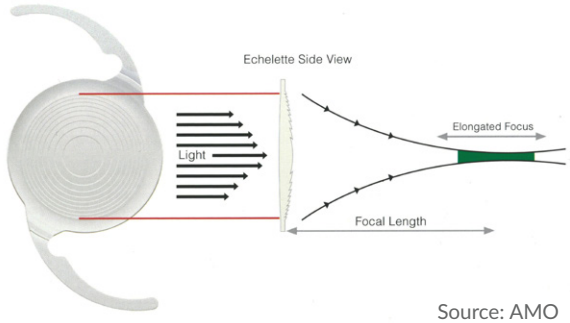
### AMO's Tecnis Symfony IOL Features Diffractive Optics

AMO received CE mark approval for its *Tecnis Symfony* Extended Range of Vision IOL in May 2014 and launched the lens in Europe last summer. The product is also available in Australia. AMO is conducting a clinical study in the US to support a submission for FDA approval. The *Symfony IOL* is available with and without toric correction for astigmatism.

Like the *TECNIS Multifocal IOL*, *Symfony* features a diffractive optical design, with a pattern of concentric circles on the lens that resembles a typical MF-IOL (*see Figure 1*). However, the size, shape, and height of the rings have been redesigned, and unlike MF-IOLs, the *Symfony* optic does not create a second focal point. The lens incorporates a proprietary diffractive "echelette" (groove) design that creates a novel pattern of light diffraction that elongates the focus of the eye, resulting in an extended range of vision. In addition, in order to address the loss of contrast sensitivity that typically occurs with multifocal optics, the lens features proprietary achromatic technology that corrects chromatic aberration and enhances contrast.

**Figure 1**

**AMO's *Tecnis Symfony* IOL**




Source: AMO

A 31-patient clinical study from New Zealand showed that *Symfony* extends the eye's depth of focus by 1 diopter versus a monofocal IOL, and delivers 20/20 or better mean visual acuity from distance to about 66 cm from the eye (about 1.5 D of defocus), which is a comfortable distance for viewing a computer monitor. Mean visual acuity of 20/40 or better is maintained down to a distance of about 40 cm (about 2.5 D of defocus), which represents a typical reading distance. Unlike typical MF-IOLs, there is no drop-off of acuity at the intermediate distance, and the incidence of glare and halos is comparable to a monofocal IOL at three months post-op. High rates of spectacle independence were reported at all distances: 100% for far vision, 94% for intermediate, and 87% for near. Patient satisfaction in the study was very high, with 97% of patients saying they would elect to have the *Symfony* IOL implanted again.

In a European multicenter study, 95-99% of patients were satisfied with overall vision, daytime and nighttime vision, and far and intermediate vision, while 73% reported good spectacle-free near vision. Most (97.6%) said they would recommend *Symfony* to friends and family. Only 5-10% reported mild/moderate halo or starbursts, and only 1-2% reported night glare or severe halos or starbursts.

Early clinical experience with *Symfony* in both New Zealand and Europe suggests that micro-monovision, or choosing an IOL power that targets about -0.5 D of myopia in one eye, may increase the rate of spectacle independence by improving bilateral near visual acuity with minimal compromise of distance acuity.

### AcuFocus IC-8 IOL Features Small Aperture Optic

The *IC-8* IOL from AcuFocus achieved CE mark approval in late 2014 and was introduced at the Congress of the European Society of Cataract and Refractive Surgeons (ESCRS) in September 2014. The company is initiating a post-market evaluation in Europe, with the goals of refining the surgical parameters and patient selection criteria in order to ensure reliable and repeatable clinical results. A larger controlled launch, in Europe and possibly other regions, could be initiated later this year. However, the company has no current plans to initiate a US clinical study this year.

Like the company's flagship product, the *KAMRA* Corneal Inlay for presbyopia, the AcuFocus *IC-8* IOL achieves extended depth of focus through the use of small aperture optics (*see Figure 2*). The lens optic contains a thin embedded mask, made from polyvinylidenefluoride (PVDF) and carbon nanoparticles, with a 1.4 mm diameter opening and a 3.2 mm outside diameter. Like the AMO *Symfony* IOL, the AcuFocus *IC-8* is designed to provide a continuous, uninterrupted range of functional near-to-distance vision, while minimizing visual side effects by not creating two competing focal points. Optical modeling suggests that the IC-8 increases depth of focus by 1.5 D to 2.0 D.

Figure 2

**AcuFocus *IC-8* IOL**

Source: AcuFocus

In a pilot study, patients achieved mean near vision of J2 (20/25). It should be noted that clinical experience with the *KAMRA Inlay* has shown that the small aperture provides the best range of vision if the eye is targeted for a small amount of myopia, corresponding to a refractive error of -0.75D. The small aperture IOL appears to work in the same way: if the treated eyes in the pilot study had been targeted for -0.75D, 89% of treated eyes would have achieved J1 (20/20) near visual acuity. At the same time, if targeted to -0.75D, all eyes would have achieved 20/25 intermediate and distance vision as well, and over half of treated eyes would have achieved 20/20 at both intermediate and distance. At 12 months, the incidence of visual symptoms such as glare and halos remains low.

Visual field and contrast sensitivity are impacted to a small degree by the *IC-8*. However, these issues are not expected to have a major impact on overall visual performance, since the lens has been implanted thus far almost entirely as a single eye implant, with a high quality monofocal IOL implanted in the other eye. Clinical experience so far with the *IC-8* suggests that patients experience functional bilateral vision across a broad near-to-far range with a single implant. As a monocular solution, the *IC-8* may prove to be a lower-cost premium option for cataract patients versus premium IOLs that are implanted bilaterally. That said, it is also possible that bilateral implantation of *IC-8* IOLs may become a viable option for some patients in the future.

### Hoya iSert Gemetric IOL Features Positive Asphericity

Hoya Surgical Optics is a leading supplier of IOLs in Japan, with a more limited market presence in other countries, including the US. The company is taking a third differentiated approach to the emerging EDOF-IOL market with its *iSert Gemetric 751* IOL with Positive Aspheric Optic. This IOL features a modification to the monofocal optic in Hoya's *iSert 251* hydrophobic acrylic preloaded IOL. The optic features a controlled positive spherical aberration designed to provide extended depth of focus. The use of controlled positive or negative spherical aberration to achieve extended depth of focus is also utilized in a number of cornea-based surgical presbyopia treatments designed to alter corneal curvature.

The *iSert Gemetric* IOL has CE mark approval and has been introduced on a limited basis in Europe. Interestingly, this IOL was approved in the US in mid-2014 via a premarket approval (PMA) supplement, but has not yet been launched on the US market, possibly due to concerns that current product labeling will hinder the company's ability to market the lens as a premium PC-IOL. Hoya has not disclosed its timeline for launching this product in the US and other markets.

## Huge Patient Populations Drive the Surgical Presbyopia Market Opportunity

Although the PC-IOL market is generally viewed as a subsegment of the cataract surgery market, these lenses are also a key product category within the presbyopia surgery market. Presbyopia is the age-related loss of near visual acuity that occurs as the eye's lens gradually loses its ability to accommodate, or adjust, to achieve near focus. Reading glasses, bifocal and trifocal spectacles, and multifocal contact lenses are the traditional means of addressing presbyopia. Presbyopia usually begins to impact near vision between the ages of 40 and 50, and nearly everyone over age 50 is affected. By the time most patients with cataracts require surgery, they have already been presbyopic for a number of years, and the implantation of a standard monofocal IOL results in the loss of any accommodative ability that may still remain in the eye's natural lens.

PC-IOLs present cataract patients with an opportunity to address their presbyopia by upgrading to a premium IOL during a medically necessary surgical procedure. However, these lenses may also be used electively in younger, pre-

cataract patients as a means of addressing the loss of near vision. Because intraocular lens-replacement surgery is considered a relatively invasive approach for younger pre-cataract patients, a number of less-invasive alternatives are under development for presbyopes who want to restore their ability to see at near and/or intermediate distances without dependence on glasses or contact lenses. These include corneal inlays, excimer laser ablations that provide increased depth-of-focus, and scleral implants (*see Figure 3*).

It is interesting to note that the EDOF approach to surgical presbyopia correction had already been incorporated into a number of presbyopia-correcting surgical technologies prior to the emergence of EDOF-IOLs. The two corneal inlay products that are most advanced in clinical development employ EDOF optics: the *KAMRA Inlay* from AcuFocus achieves EDOF via small aperture optics, and the *Raindrop Near Vision Inlay* from **ReVision Optics Inc.** achieves EDOF via subtle changes in corneal curvature. In addition, presby-LASIK treatments from Carl Zeiss Meditec (*PRESBYOND Laser Blended Vision*) and Bausch + Lomb (*SUPRACOR*) both aim to extend depth-of-focus through changes in corneal curvature.

Figure 3

**Selected Pipeline Products: Surgical Presbyopia Correction**

| Company: *Product* | Description | Development Status |
|---|---|---|
| **Extended Depth of Focus (EDOF) IOLs** | | |
| Abbott Medical Optics: *Symfony IOL* | EDOF via diffractive optics | CE mark approved; marketed in Europe; US clinical study underway |
| AcuFocus: *IC-8 IOL* | EDOF via small aperture optics | CE mark approved; post-market evaluation in Europe |
| Hoya Surgical Optics: *Gemetric 751 IOL* | EDOF via positive spherical aberration | CE mark approved; marketed in Europe; FDA-PMA approved but not yet marketed in US |
| **Accommodating IOLs** | | |
| PowerVision: *FluidVision Accommodating IOL* | Accommodation via fluid transfer within the IOL | Clinical study underway to support CE mark approval |
| **Corneal Inlays** | | |
| AcuFocus: *KAMRA Inlay* | EDOF via small aperture optics | CE mark approved; PMA submitted and positive recommendation at FDA panel meeting |
| ReVision Optics: *Raindrop Near Vision Inlay* | EDOF via corneal curvature (prolate cornea) | CE mark approved; enrollment completed in US IDE study |
| Presbia: *Flexivue Microlens* | Multifocal optic | CE mark approved; US IDE study underway |
| **LASIK for Presbyopia Correction** | | |
| Carl Zeiss Meditec: *PRESBYOND Laser Blended Vision* | EDOF via corneal curvature and micro-monovision using excimer laser | CE mark approved |
| Bausch + Lomb: *SUPRACOR* | EDOF via corneal curvature using excimer laser | CE mark approved |
| **Scleral Implants** | | |
| Refocus Group: *VisAbility Implant System* | EDOF and restoration of accommodative function | CE mark approved; enrollment completed in US IDE study |

Source: EyeQ Research

The pool of patients who are potential candidates for surgical presbyopia correction is enormous and growing. There are approximately 2.3 billion presbyopes worldwide, including about 700 million in developed countries. By 2020, there will be approximately 306 million presbyopes in the 45-64 pre-cataract age group in 13 of the most developed markets of the Americas, Europe, and Asia.

Presbyopes in this age group who live in these countries would be considered the most addressable candidates for elective surgical procedures. This group is divided roughly equally among people with myopia (nearsightedness), hyperopia (farsightedness), and emmetropia (absence of refractive error). In addition, by 2020, approximately 27 million people will have undergone cataract surgery within the previous five years and would also be candidates for surgical presbyopia correction, bringing the total eligible population in these countries to about 333 million (*see Figure 4*.)

Among the 203 million myopic and hyperopic presbyopes age 45-64 in the most developed markets, two patient subsets are worth noting. By 2020, roughly 13 million patients in this group will have already undergone laser vision correction, including LASIK, to correct their distance vision. These post-refractive surgery patients should be prime candidates for surgical presbyopia correction, since they have chosen to undergo a vision correction procedure previously and are likely to be pleased with their results given the high satisfaction rates associated with LASIK.

In addition, approximately 300,000 myopic and hyperopic presbyopes in the 45+ age group are expected to undergo LASIK each year, and these patients may choose to upgrade their refractive correction procedure to one that addresses near vision in addition to distance vision. LASIK has a long and successful history of procedure upgrades, including custom/wavefront ablations and all-laser techniques. Although this is the smallest of the eligible populations shown in Figure 4, refractive surgeons should be able to upgrade a relatively high percentage of their presbyopic LASIK patients to one of the emerging presbyopia correction technologies.

The other important presbyopia surgical upgrade opportunity consists of the 5.7 million people in 2020 who are projected to undergo cataract surgery in these countries. It is these 5.7 million cataract patients who are the primary candidates for PC-IOLs, including the new EDOF lenses.

## Surgical Presbyopia Correction: A $2 Billion Market Opportunity

Surgical correction of presbyopia represents a $2 billion annual market opportunity, based on 2020 populations in 13 of the most active refractive surgery markets (*see Figure 5*). Roughly half, or $1 billion, consists of cataract surgery procedures upgraded to include PC-IOLs, assuming 10% penetration of 5.7 million cataract patients, bilateral treatment in all patients, and a $900 average selling price (ASP) for PC-IOLs. Although 10% procedure penetration is roughly double the current PC-IOL penetration rate, there is significant upside potential in this market segment resulting from further evolution of self-pay policies globally and new PC-IOL technologies, including EDOF lenses and more advanced accommodating IOLs.

The LASIK upgrade opportunity is approximately $120 million, based on 30% penetration of the 300,000 presbyopic patients that elect to have LASIK surgery annually. Presbyopia-correcting technologies that address LASIK patients include corneal inlays and modified LASIK ablation profiles that provide extended depth of focus. Because some of these technologies are designed as monocular (single-eye) treatments and others are designed to be used bilaterally, it is assumed that about half of patients would receive bilateral treatment.

Finally, the 333 million presbyopes aged 45-64 in the most developed refractive surgery markets represent an additional opportunity of nearly $1 billion annually. This is based on assumed penetration of only 0.2% of this population annually, 50% bilateral treatment, and a $900 ASP. In addition to corneal inlays and presby-LASIK, these patients could also be treated with PC-IOLs or scleral implants.

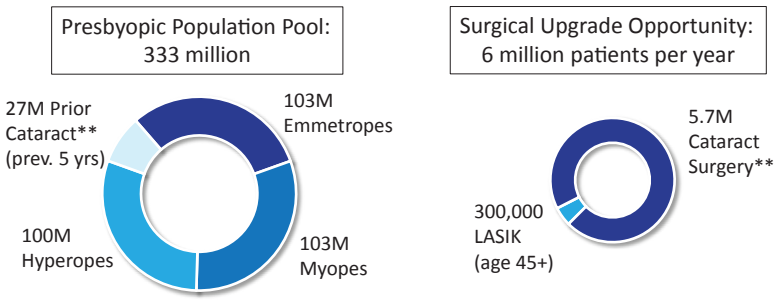
For historical context, the annual market penetration rate for LASIK over the past 15 years has averaged about 0.4% of eligible myopes and hyperopes each year in these more developed markets. The 0.2% annual penetration rate illustrated in Figure 5 is roughly half of the historical LASIK penetration rate. This assumes that the presbyopic population will be harder for refractive surgeons to reach, given the fact that so many of the eligible presbyopes are also emmetropes, and have not required spectacles or contact lenses for vision correction prior to the onset of presbyopia. If this assumption turns out to be too conservative and presbyopes adopt surgical correction at the historical rate for LASIK, the annual presbyopia market opportunity could be closer to $3 billion.

*Michael Lachman is president of EyeQ Research, which provides strategic advisory and market research/analytics to the ophthalmic industry. He is a Contributing Writer for* The MedTech Strategist. *(Email: Michael@EyeQResearch.com)*

Figure 4

### Presbyopic Populations Eligible for Surgical Correction

13 Developed Countries*, Age 45-64**, Year 2020




*13 countries included: Americas (US, Canada, Argentina, Brazil, Colombia), Europe (France, Germany, Italy, Spain, UK), Asia-Pacific (Japan, South Korea, Australia)

** Cataract surgery and prior cataract populations not limited to age 45-64

Source: EyeQ Research

Figure 5

### Market Opportunity for Surgical Presbyopia Correction

13 Developed Countries*, Year 2020

| Patient Segment | Patient Pop. | Annual Potential Penetration | Pct. Bilateral | Potential Annual Eyes Treated | Annual Market Potential |
|---|---|---|---|---|---|
| Cataract Surgery | 5.7M/yr | 10% upgrade | 100% | 1.14M | $1.0B |
| LASIK (age 45+) | 300K/yr | 30% upgrade | 50% | 135,000 | $120M |
| Other Presbyopes | 333M | 0.2% | 50% | 1.0M | $900M |

Market potential based on $900 average price per eye for products (implants or laser)

Primary presbyopia technology for cataract surgery: Presbyopia-correcting IOLs (PC-IOLs)

Technologies for other patient segments: Corneal inlays, presby-LASIK, PC-IOLs, scleral implants

*13 countries included: Americas (US, Canada, Argentina, Brazil, Colombia), Europe (France, Germany, Italy, Spain, UK), Asia-Pacific (Japan, South Korea, Australia)

Source: EyeQ Research